

Dairy Consumption and the Incidence of Hyperglycemia and the Metabolic Syndrome

Results from a French prospective study, Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR)

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THE DATA FROM THE EPIDEMIOLOGICAL

STUDY ON THE INSULIN RESISTANCE

SYNDROME (DESIR) STUDY GROUP³

OBJECTIVE—In the French Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort, cross-sectional analyses have shown that a higher consumption of dairy products and calcium are associated with a lower prevalence of the metabolic syndrome (MetS). We assess the influence of dairy products on 9-year incident MetS and on impaired fasting glycemia and/or type 2 diabetes (IFG/T2D).

RESEARCH DESIGN AND METHODS—Men and women who completed a food frequency questionnaire at baseline and after 3 years were studied ($n = 3,435$). Logistic regression models were used to study associations between the average year 0 and year 3 consumption of milk and dairy products, cheese, dietary calcium density, and incident MetS and IFG/T2D after adjusting for 1) sex, age, alcohol, smoking, physical activity, fat intake and 2) additionally for BMI. Associations between dairy products and continuous variables were studied by repeated-measures ANCOVA, using the same covariates.

RESULTS—Dairy products other than cheese, and dietary calcium density, were inversely associated with incident MetS and IFG/T2D; cheese was negatively associated with incident MetS. All three parameters were associated with lower diastolic blood pressure, and with a lower BMI gain. Higher cheese intake and calcium density were associated with a lower increase in waist circumference and lower triglyceride levels. Calcium density was also associated with a lower systolic blood pressure and a lower 9-year increase in plasma triglyceride levels.

CONCLUSIONS—A higher consumption of dairy products and calcium was associated with a lower 9-year incidence of MetS and IFG/T2D in a large cohort drawn from the general population.

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The metabolic syndrome (MetS) is a cluster of metabolic disorders, including central obesity, glucose intolerance (impaired fasting glucose [IFG], impaired glucose tolerance, type 2 diabetes), dyslipidemia (low HDL cholesterol [HDL-C], high triglyceride levels), and high blood pressure. All of its components are risk

factors for cardiovascular disease (CVD). Although fats from dairy products are rich in saturated fatty acids, there is no clear evidence that dairy food is associated with a high risk of CVD (1). An explanation is that dairy consumption has been found to be inversely associated with MetS traits in cross-sectional as well as prospective studies. In the French population from the Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort, cross-sectional analyses have shown that a higher consumption of dairy products or calcium was associated with a lower prevalence of the MetS (2,3). In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the highest consumption of dairy products was associated with a 70% reduction in the risk of incident MetS over a period of 10 years, when compared with the group with the lowest consumption (4). However, these results were not always found. In an elderly Dutch population from the Hoorn Study with a 6.4-year follow-up, a higher dairy consumption did not protect against weight gain or the development of metabolic disturbances (5). The aim of our study was to assess the influence of dairy products on the 9-year cumulative incidence of the MetS and IFG and/or type 2 diabetes (IFG/T2D) as well as on associated traits, in the French population-based prospective study with a 9-year follow-up, DESIR.

RESEARCH DESIGN AND METHODS

The DESIR study is a prospective study of 5,212 subjects at inclusion (2,576 men and 2,636 women, aged 30–65 years), recruited from volunteers who were offered periodic health examinations free of charge by the French Social Security system in 10 health examination centers from the western part of France. They were clinically and biologically evaluated at visits every 3 years, and the final examination was 9 years after inclusion. For the purpose of these analyses,

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See accompanying editorial, p. 1064.

diabetic subjects at entry were excluded. In addition, subjects who declared that they were on a diet and those who did not answer all the questions in the food frequency questionnaire were excluded. In consequence, the 3,435 subjects (1,710 men, 1,725 women) with a food frequency questionnaire at baseline and/or at 3 years remained for this study. The study was approved by the ethics committee of the Kremlin Bicêtre Hospital, and all participants signed an informed consent.

Measurements

Weight, height, and waist circumferences were measured by trained personnel. Venous blood samples were collected in the morning after subjects had fasted for 12 h. Systolic and diastolic arterial pressures were measured with a mercury sphygmomanometer adapted for arm size after 5 min of rest with participants in a supine position. Two measures of blood pressure were taken, and means were used for the analysis. A detailed description of laboratory measurements including fasting triglycerides, HDL-C, glucose, and insulin is provided elsewhere (6).

In the present work, two definitions for the MetS were used. According to the International Diabetes Federation (7), it was defined as waist circumference $\geq 94/80$ cm for men/women plus two of the following factors: 1) elevated triglycerides: ≥ 1.70 mmol/L or specific treatment for this lipid abnormality; 2) reduced HDL-C: ≤ 1.03 mmol/L for men and 1.29 mmol/L for women or specific treatment for this lipid abnormality; 3) elevated blood pressure: $\geq 130/85$ mmHg or treatment of previously diagnosed hypertension; and 4) elevated fasting glycemia ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes (treated by glucose lowering drugs and/or fasting glycemia ≥ 7.0 mmol/l). According to the National Cholesterol Education Program-Adult Treatment Panel III (8), it was defined as three of the following factors: 1) waist circumference $> 102/88$ cm for men/women; 2) elevated triglycerides: ≥ 1.70 mmol/L; 3) reduced HDL-C: ≤ 1.03 mmol/L for men and 1.29 mmol/L for women; 4) elevated blood pressure: systolic blood pressure ≥ 130 or diastolic ≥ 85 mmHg; and 5) elevated fasting glycemia ≥ 6.1 mmol/L.

Type 2 diabetes was defined as fasting plasma glucose ≥ 7 mmol/L or treatment by antidiabetic agents. IFG was defined as fasting plasma glucose between 6.1 and 6.9 mmol/L. Incident cases for MetS

and/or IFG/T2D were defined as subjects free of disease at entry who developed the disease at any time during the follow-up.

A 23-item questionnaire was completed by each participant to determine the frequency and level of consumption of different foods. This questionnaire has been validated by comparison with the dietary history method consisting of 30-min interviews by trained dietitians. This validation study enabled the determination of multiple linear regression equations to estimate the main nutrient intakes (including calcium) from the questions on the consumption of different foods (9). Two groups of dairy products were defined: cheese or milk and other dairy products (except cheese). One portion was defined as 30 g for cheese, and 125 mL for milk or milk products. There were four responses for the intake of dairy products (never; < 1 portion/day; 1–2 /day; > 2 /day; coded 1,2,3,4) and 3 for cheese intake (0–1 portion/day; 2–3 /day; > 3 /day; coded 1,2,3). Calcium density of the diet was defined as the amount of calcium ingested per 1,000 kCal (excluding alcohol).

Statistics

Analyses used the average dietary data from year 0 and year 3 to take into account the variability over time; 212 participants with only one dietary record were also included; their exclusion did not change the results. We categorized the dairy intake and the cheese intake in 4 groups and 3 groups, respectively, according to their responses to both questionnaires. The dairy intake groups were defined as group 1 for an average response ≤ 2 , group 2 for an average response of 2.5, group 3 for an average response of 3, and group 4 for an average response > 3 . The cheese intake groups were defined as group 1 for an average response of 1, group 2 for an average response of 1.5, and group 3 for an average response ≥ 2 . These limits were chosen in order to have comparable frequencies in the groups. For calcium, we calculated sex-specific quartiles of the mean calcium density at year 0 and year 3 (3). Multiple logistic regression analysis was used to evaluate associations between the dairy consumption variables, and the odds of developing MetS or IFG/T2D during the 9-year study. Two models were used: in model 1, the covariates were age, sex, alcohol consumption (continuous covariate), smoking (yes/no), physical activity (three

classes used as a continuous covariate), fat intake (from the questions on the consumption of meat, fish, pork products, fried foods, butter, cheese, and other dairy products); in model 2, the same covariates as well as BMI as a covariate. To take into account the variation in BMI over the 9 years, we used as covariate the mean of BMI at entry and at 9 years. Odds ratios indicate the risk of a change from one category to the next, e.g., from one quartile of calcium density to the next quartile. ANCOVA with repeated measures was used to test for the average effect of dairy products and the effects on changes between baseline and the end of the follow-up (9 years), adjusted for age, sex, alcohol, smoking, physical activity, fat intake, and BMI. Data were log transformed for skewed variables (insulin levels, serum triglycerides). Results are presented as least squares means adjusted for covariates with the SEM, or as geometric means with 95% CI for skewed variables.

RESULTS—The consumption of dairy products other than cheese and the calcium density of the diet were inversely associated with the incidence of the MetS, whatever the definition, and with the incidence of IFG/T2D during the 9-year follow-up (Table 1). The consumption of cheese was negatively associated with the incidence of the MetS (Table 1). The consumption of dairy products other than cheese was associated with the incidence of type 2 diabetes alone (multiple adjustment without BMI, model 1: odds ratio 0.82 [95%CI 0.71–0.92]; $P = 0.02$), but this association was no longer significant after taking BMI into account (model 2, $P = 0.07$). Neither cheese nor calcium density were associated with type 2 diabetes alone (data not shown). No interaction with sex was observed nor with overweight at baseline.

The three dairy parameters were associated with lower 9-year diastolic blood pressure and with lower BMI gain over this period (Supplementary Table A1–3). Higher cheese intake and calcium density were associated with lower triglyceride levels and a lower 9-year increase in waist circumference both in men and women (Supplementary Tables A2 and 3). Calcium density was also associated with a lower systolic blood pressure and a lower 9-y increase in plasma triglycerides levels (Supplementary Table A3). Few significant interaction effects with sex were observed: time changes in systolic blood

Table 1—Incidence of the MetS and IFG/T2D according to dairy product consumption in the DESIR cohort

	No incident MetS (IDF)	Incident MetS (IDF)	No incident MetS (NCEP)	Incident MetS (NCEP)	No incident IFG/T2D	Incident IFG/T2D
Dairy products (except cheese)						
Group 1 (low)	430 (69.2)	191 (30.8)	568 (81.5)	129 (18.5)	543 (77.5)	158 (22.5)
Group 2	423 (75.3)	139 (24.7)	525 (84.1)	99 (15.9)	522 (83.8)	101 (16.2)
Group 3	960 (81.4)	220 (18.6)	1,111 (87.3)	162 (12.7)	1,126 (87.0)	169 (13.1)
Group 4 (high)	525 (81.8)	117 (18.2)	608 (90.7)	62 (9.3)	607 (89.1)	74 (10.9)
Unadjusted	0.77 (0.71–0.84); $P < 10^{-6}$		0.78 (0.70–0.85); $P < 10^{-6}$		0.74 (0.68–0.81); $P < 10^{-6}$	
Model 1†	0.86 (0.79–0.94); $P = 0.001$		0.84 (0.76–0.93); $P = 0.0007$		0.83 (0.75–0.92); $P = 0.0003$	
Model 2‡	0.88 (0.79–0.97); $P = 0.01$		0.89 (0.79–1.00); $P = 0.04$		0.85 (0.76–0.94); $P = 0.001$	
Cheese						
Group 1 (low)	718 (76.7)	218 (23.3)	847 (85.2)	147 (14.8)	868 (85.5)	147 (14.5)
Group 2 (medium)	511 (76.5)	157 (23.5)	636 (86.2)	102 (13.8)	639 (85.7)	107 (14.3)
Group 3 (high)	1,109 (79.2)	292 (20.8)	1,329 (86.7)	203 (13.3)	1,291 (83.9)	248 (16.1)
Unadjusted	0.93 (0.84–1.02); $P = 0.14$		0.94 (0.84–1.05); $P = 0.28$		1.07 (0.96–1.19); $P = 0.23$	
Model 1†	0.90 (0.80–1.00); $P = 0.06$		0.86 (0.76–0.98); $P = 0.02$		0.94 (0.83–1.07); $P = 0.37$	
Model 2‡	0.88 (0.77–1.00); $P = 0.05$		0.82 (0.71–0.95); $P = 0.008$		0.93 (0.82–1.06); $P = 0.30$	
Calcium density						
Quartile 1	553 (74.6)	188 (25.4)	668 (82.8)	139 (17.2)	676 (81.8)	150 (18.2)
Quartile 2	576 (75.7)	185 (24.3)	716 (86.6)	111 (13.4)	709 (84.3)	132 (15.7)
Quartile 3	601 (79.7)	153 (20.3)	707 (85.0)	125 (15.0)	696 (84.6)	127 (15.4)
Quartile 4	608 (81.2)	141 (18.8)	721 (90.4)	77 (9.6)	717 (88.5)	93 (11.5)
Unadjusted	0.87 (0.81–0.94); $P = 0.0005$		0.84 (0.77–0.92); $P = 0.0001$		0.85 (0.78–0.93); $P = 0.0003$	
Model 1†	0.90 (0.82–0.97); $P = 0.009$		0.86 (0.78–0.94); $P = 0.001$		0.91 (0.83–1.00); $P = 0.05$	
Model 2‡	0.86 (0.78–0.95); $P = 0.002$		0.83 (0.75–0.92); $P = 0.001$		0.90 (0.82–0.99); $P = 0.04$	

Data are n (%) or odds ratio (95% CI) unless otherwise indicated. Odds ratios were calculated by logistic regression and indicate the risk for a change from one category to the next. IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program. †Model 1: adjustment for sex, age, smoking, total fat intake, physical activity. ‡Model 2: same as model 1 plus adjustment for mean BMI (mean of BMI at baseline and at 9 years of follow-up).

pressure for dairy intake (Supplementary Table A1), and insulin levels for calcium density (Supplementary Table A3), which were significant only in women. Some adverse effects were observed. Intake of dairy products was associated with lower HDL-C levels in men, but the decrease with time was also lower. Intake of cheese was associated with a higher average BMI, but also with a lower increase with time.

CONCLUSIONS—In the DESIR prospective study with a 9-year follow-up, we found that the consumption of dairy products and cheese as well as dietary calcium density, were associated with a lower incidence of the MetS. The consumption of dairy products, cheese excluded, and calcium intake, were also associated with a lower incidence of IFG or type 2 diabetes. When looking at phenotypes associated with the MetS, these parameters were also generally associated with a more beneficial profile during the follow-up, or with a better change in profile over the 9-year period. These results support the hypothesis of beneficial effects of milk products on cardiovascular risk, despite their saturated fat content. In a meta-analysis of

prospective studies (10), it was shown that milk and dairy consumption was associated with a lower risk of incident vascular events. This might be explained by beneficial associations with the MetS and associated parameters and/or type 2 diabetes, such as those found in the current study and by other groups. In this respect, Warensjö et al. (11) found, in a prospective study, a negative association between the risk of myocardial infarction and biomarkers of milk fat, which disappeared when adjusted for variables related to the MetS (diabetes, blood pressure, BMI).

Our results are consistent with those obtained in the prospective Atherosclerosis Risk in Communities (ARIC) study (12) where subjects in the highest quintile of dairy consumption had a 13% lower risk of the MetS when compared with the lowest quintile. In another prospective study, CARDIA (4), results were similar, but only in the overweight. As stated in the paper by Lutsey et al. (12), the differences between studies may be the result of different methods used, for example definition of outcome, population, age, dietary assessment, and statistical methods. Both the DESIR and the ARIC studies were in the middle-aged,

but the CARDIA study was in young adults, aged 18–30 years.

In prospective studies, for men with a 12-year follow-up (13), as in women with a 10-year follow-up (14), there was a negative association between dairy intake and type 2 diabetes incidence. In these two studies, the association with dairy was mainly due to low-fat dairy. Unfortunately, we do not have specific data on low-fat or high-fat dairy products in our study, but we believe that our results are in accordance with this differential effect as dairy products included milk which is consumed as 80% low-fat and are associated beneficially with IFG/T2D, whereas cheese, which is high-fat, is not significantly associated with IFG/T2D risk. In the Nurses Health Study (15), women who consumed three or more servings per day had an 11% lower risk of type 2 diabetes compared with women who consumed less than one serving per day of dairy. After adjustment for total vitamin D and calcium intake, this association was attenuated, showing that the association with dairy food was due in large part to these nutrients. In DESIR study, the calcium density of the diet was also very significantly associated

with IFG/T2D and the MetS, but since it was not directly measured but only calculated from food intake mainly from dairy variables (therefore very linked to the assessment of dairy intake), we could not adjust for this variable in order to test whether the beneficial effects of dairy were due to calcium in DESIR. Unfortunately, we do not have data on vitamin D. Compounds other than calcium and vitamin D may be involved in these associations: peptides or conjugates of linoleic acid (1,16,17).

Dairy consumption and calcium intake have been described in epidemiological studies to be associated with lower BMI or to lower body weight in intervention studies, in humans as well as in animal models (18,19). In our longitudinal study, we did not find an overall association with BMI, but there was a lower increase in BMI and/or waist circumference over the 9-year follow-up. A similar finding was found in the CARDIA study (4), in which high dairy intake appeared to protect against weight gain. In contrast, this result was not found in the Hoorn Study (5). In the French Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study, a high consumption of dairy products was associated with a lower weight gain over 6 years, but this result was obtained only in overweight men (20). In the DESIR study, no significant interaction with sex was found for BMI changes, but we observed a significantly lower BMI increase only in men ($P = 0.07, 0.05, \text{ and } 0.002$ for dairy products, cheese, and calcium density respectively). The effects on BMI did not explain all of the effects on the MetS, as we adjusted for BMI in all our analyses.

Modest but significant effects on triglycerides were found. Nevertheless, no beneficial effect on HDL-C was observed. These results are very similar to those from the CARDIA study (4). The adjustments that we systematically used—BMI, fat intake, physical activity and alcohol—might have lessened or cancelled these associations. Here we observed a negative association between cheese and triglycerides which has been found sometimes (21,22), but not always (23,24), in cross-sectional studies.

Dairy consumption has generally been associated with low blood pressure. This was found in the cross-sectional analysis of the Hoorn Study (24) but not in the prospective data (5). In our study, only the mean effect was found to be significant, but generally there was no effect on changes. Dairy nutrients, notably

calcium, have been shown to have a blood pressure lowering effect. Dairy peptides may also act as ACE inhibitors (16)

Consistently with the results concerning the MetS and/or IFG/T2D, we found a negative association between the calcium density of the diet and insulin levels. This association, which was detected only in women, might be explained by the higher dietary calcium density in women than in men (3). A negative trend was also found with cheese intake ($P = 0.07$). In acute effect, milk intake has been associated with higher insulin levels due to insulin-secretaagogue peptides; nevertheless, its chronic effect has rather been linked to an improvement in insulin sensitivity and thus, presumably, with lower insulinemia. Dairy foods may beneficially alter adiponectin levels independently of changes in body weight (18). This in turn may increase insulin sensitivity and lower insulin levels. It has also been observed that milk and whey appear insulinotropic as an acute effect but that the addition of fermented milk (yogurt) lowered postprandial insulin and glucose as compared with a reference meal alone (17). Moreover, whey protein was associated with a 40% lower plasma insulin after 6 weeks in insulin-resistant rats (17). Biomarkers of milk fat were also negatively associated with plasma insulin (25).

There was no significant interaction between dairy variables and sex on the risk of the MetS or on IFG/T2D (actually the results were very similar [data not shown]), and very few significant interactions were observed for associations with continuous variables.

Our study has several strengths but also some limitations. Among the strengths are the prospective nature of the data and the large number of participants included, who were from the general population, and selected with a 1:1 sex ratio and in age strata. We were also able to adjust for confounders such as lifestyle factors. The relationships we observed with the characteristics of the MetS are modest, but they were obtained after adjustment for lifestyle variables, including physical activity, smoking, alcohol consumption, and dietary fat intake. Moreover, the adjustments for BMI show that there may be a specific independent effect of dairy intake on the MetS characteristics. The main limitation of our study concerns the dietary questionnaire. We used a very simple semiquantitative self-questionnaire. Nevertheless, it has been validated by a more sophisticated

questionnaire (9) and is suitably short to be well answered in an epidemiological study. As with all food-frequency questions, the accuracy of the responses (under- or over-consumption) is difficult to evaluate. We may have over-evaluated the consumption of calcium with a semi-quantitative questionnaire, but the range of our values is not too far removed from the range of intake observed in the 1998–1999 cross-sectional French Enquete INCA (Individuelle et Nationale sur les Consommations Alimentaires) food consumption survey (3). We have used the same food frequency questionnaire, completed at baseline and at the 3-year visit, and using mean values will reduce the variability of the responses. Our questionnaire does not allow the separation of low-fat and high-fat products, or to estimate the effects of the different dairy products. However, we could separate cheese from other dairy products. As already stated, it can be assumed that in France, cheese is high-fat, but that the milk included in other dairy products is low fat.

In summary, a higher consumption of dairy products and calcium was associated with a lower incidence of the MetS and IFG/T2D during a 9-year follow-up period, in a large cohort drawn from the French general population. This inverse association was observed with many traits of the MetS. These results indicate that dairy product consumption could be associated with a lower cardiovascular risk.

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F.F. researched data and wrote and reviewed the manuscript. A.L., C.A.K., R.J., and I.P.-B. researched data and contributed to discussion. O.L. and S.V. researched data and reviewed and edited the manuscript. B.B. and M.M. researched data, contributed to discussion, and reviewed and edited the manuscript.

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